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 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
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 NEWS 19  Aug 09  JAPIO to be reloaded August 18, 2002

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 NEWS WWW      CAS World Wide Web Site (general information)
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=> s hirudin and peg
L1          226 HIRUDIN AND PEG

=> s l1 and (extracorporeal or renal or dialysis or hemodialysis)
L2           20 L1 AND (EXTRACORPOREAL OR RENAL OR DIALYSIS OR HEMODIALYSIS)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           13 DUP REM L2 (7 DUPLICATES REMOVED)

=> s l1 and (half (w) life)
L4           33 L1 AND (HALF (W) LIFE)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           11 DUP REM L4 (22 DUPLICATES REMOVED)

=> s l3 and l5
L6            1 L3 AND L5

=> s l3 or l5
L7           23 L3 OR L5

=> d hist

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     16 AUG 2002
L1           226 S HIRUDIN AND PEG
L2            20 S L1 AND (EXTRACORPOREAL OR RENAL OR DIALYSIS OR HEMODIALYSIS)
L3            13 DUP REM L2 (7 DUPLICATES REMOVED)
L4            33 S L1 AND (HALF (W) LIFE)
L5            11 DUP REM L4 (22 DUPLICATES REMOVED)
L6             1 S L3 AND L5
L7            23 S L3 OR L5

=> d l7 1-23 py au ti so ab

L7   ANSWER 1 OF 23  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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09921880

PY 2001
AU Stein, G. (1); Poschel, K. A.; Bucha, E.; Ulbricht, K.; Esslinger, H. U.; Nowak, G.
TI Anticoagulant efficacy of **PEG-Hirudin** in patients on chronic intermittent **hemodialysis**.
SO Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 364A. http://www.jasn.org/. print.
Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001
ISSN: 1046-6673.

L7 ANSWER 2 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 2000
AU Poeschel, Katrin Annett; Bucha, Elke; Esslinger, Hans-U.; Noertersheuser, Peter; Jansa, Ute; Schindler, Sabine; Nowak, Goetz; Stein, Guenter (1)
TI Pharmacodynamics and pharmacokinetics of polyethylene glycol-**hirudin** in patients with chronic **renal** failure.
SO Kidney International, (December, 2000) Vol. 58, No. 6, pp. 2478-2484. print.
ISSN: 0085-2538.
AB Background. **Hirudin** selectively inhibits thrombin without co-factors and is eliminated via the kidneys. Recombinant **hirudin** (r-hi) has a terminal elimination **half-life** (t1/2) of about 50 to 100 minutes. Coupling of polyethylene glycol (**PEG**) to r-hi, giving **PEG-hirudin** (**PEG**-Hi), prolongs its t1/2 while enhancing efficacy. We looked at the pharmacodynamic and pharmacokinetic behavior of **PEG**-Hi in patients with impaired **renal** function. Methods. Anticoagulant activity and the pharmacokinetic parameters of a single intravenous bolus injection of 0.05 mg/kg body weight **PEG**-Hi were studied in 38 subjects. They were assigned to five groups: group IA, creatinine clearance (Ccr) gtoreq 80 mL/min, 8 healthy volunteers; group IB, CCr gtoreq 80 mL/min, 8 patients with normal **renal** function); group II, CCr 79 to 50 mL/min, 7 patients with mild chronic **renal** failure (CRF); group III, CCr 49 to 20 mL/min, 10 patients with moderate CRF; and group IV, CCr ltoreq 19 mL/min, 5 patients with severe CRF. Plasma and urine samples were collected from patients for up to 120 hours after dosing and from healthy volunteers for up to 24 hours. Results. **PEG**-Hi was well tolerated in all groups. No serious adverse events were noted. Cmax values were similar in all groups; area under the curve (AUC) increased in patients from 2.9 +- 1.0 mug cntdot h/mL (IB) to 21.3 +- 5.0 mug h/mL (IV). According to the severity of **renal** function, t1/2 was prolonged from 2 hours (IB) to 38.4 hours (IV), while total body clearance (CTB), **renal** clearance (CRenal), and recovery of **PEG**-Hi in the urine (FEo-t) decreased as follows: CTB from 23.3 +- 6.6 (IB) to 2.9 +- 0.6 mL/min (IV), CRenal from 7.8 +- 5.0 (IB) to 0.8 +- 0.5 mL/min (IV), and FEo-t from 40.2 +- 18.9% (IB) to 12.6 +- 13.0% (IV). Total plasma clearance of **PEG**-Hi was well correlated with CCr. Anti-IIa activity of **PEG**-Hi showed a closer linear relationship to ecarin clotting time than to activated partial thromboplastin time. Conclusion. Hence, **PEG**-Hi is considered safe in patients with CRF, but dosing and/or dose intervals should be adjusted according to the severity of **renal** impairment. Ecarin clotting time is well suited for safe and reliable monitoring of **PEG**-Hi.

L7 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1999
AU Bossavy, J. P.; Sakariassen, K. S.; Rubsamen, K.; Thalamas, C.; Boneu, B.; Cadroy, Y. (1)

09921880

TI Comparison of the antithrombotic effect of **PEG-hirudin** and heparin in a human ex vivo model of arterial thrombosis.
SO Arteriosclerosis Thrombosis and Vascular Biology, (May, 1999) Vol. 19, No. 5, pp. 1348-1353.
ISSN: 1079-5642.
AB Polyethylene glycol (**PEG**)-**hirudin** is a derivative of **hirudin** with a long plasma **half-life**. We have compared the efficacy of **PEG-hirudin** with unfractionated heparin (UH) in preventing arterial thrombosis. Arterial thrombus formation was induced ex vivo in 12 healthy human volunteers by exposing a tissue factor-coated coverslip positioned in a parallel-plate perfusion chamber to flowing nonanticoagulated human blood drawn directly from an antecubital vein at an arterial wall shear rate of 2600 s-1 for 3.5 minutes. **PEG-hirudin**, UH, or saline (as control) were administered ex vivo through a heparin-coated mixing device positioned proximal to the perfusion chamber. Platelet and fibrin deposition was quantified by immunoenzymatic measure of the P-selectin and D-dimer content of dissolved plasmin-digested thrombi, respectively. UH was administered to a plasma concentration of 0.35 IU/mL. This concentration prolonged the activated partial thromboplastin time from 32+-1 seconds to 79+-4 seconds ($P<0.01$). UH did not significantly prevent platelet deposition. However, fibrin deposition was reduced by 39% ($P<0.05$). **PEG-hirudin** in plasma concentrations of 0.5, 2.5, and 5 mug/mL prolonged the activated partial thromboplastin time to 48+-2, 87+-4, and 118+-4 seconds, respectively. In contrast to UH, **PEG-hirudin** prevented both platelet and fibrin deposition in a dose-dependent manner with a >80% reduction at 5 mug/mL ($P<0.01$). Furthermore, the plasma level of **PEG-hirudin** required to significantly prevent fibrin deposition (0.5 mug/mL) corresponded to a much shorter prolongation of activated partial thromboplastin time (48+-2 seconds) than that needed for UH (79+-4 seconds). Thus, our results are compatible with the view that thrombin is greatly involved in recruitment of platelets in evolving thrombi, and that **PEG-hirudin** is an effective agent for preventing arterial thrombosis in a human ex vivo experimental model.

L7 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1998
AU Esslinger, H.-U. (1); Bucha, E.; Poeschel, K.; Jansa, U.; Schindler, S.; Stein, G.; Nowak, G.
TI Pharmacokinetics of **PEG-hirudin** in subjects with various degrees of **renal** function.
SO Annals of Hematology, (1998) Vol. 76, No. SUPPL. 1, pp. A97.
Meeting Info.: 42nd Annual Meeting of the Gesellschaft fuer Thrombose- und Haemostaseforschung (Society for Thrombosis and Hemostasis Research) Frankfurt/Main, Germany February 25-28, 1998 Society for Thrombosis and Hemostasis Research
. ISSN: 0939-5555.

L7 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1998
AU Stein, G.; Bucha, E.; Poeschel, K.; Jansa, U.; Schindler, S.; Esslinger, H. U.; Nowak, G.
TI Pharmacokinetics of **PEG-Hirudin** in patients with chronic **renal** failure.
SO Nephrology Dialysis Transplantation, (June, 1998) Vol. 13, No. 6, pp. A6.
Meeting Info.: Annual Congress of the European Renal Association, European Dialysis and Transplant Association Rimini, Italy June 6-9, 1998 European Dialysis and Transplant Association
. ISSN: 0931-0509.

L7 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1997
AU Stein, G. (1); Bucha, E.; Poeschel, K.; Jansa, U.; Schindler, S.; Esslinger, H. U.; Nowak, G.
TI Pharmacokinetics of **PEG-hirudin** in patients with chronic **renal** failure.
SO Journal of the American Society of Nephrology, (Sept., 1997) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 77A.
Meeting Info.: 30th Annual Meeting of the American Society of Nephrology San Antonio, Texas, USA November 2-5, 1997 American Society of Nephrology . ISSN: 1046-6673.

L7 ANSWER 7 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1997
AU Humphries, Julia (1); Lattimer, Christopher; Smith, Alberto; McGuinness, Catharine L.; Whitton, Colin; Gaffney, Patrick J.; Burnand, Kevin G.
TI High and constant plasma levels of tissue plasminogen activator and **PEG-hirudin** can be achieved by subcutaneous delivery.
SO Thrombosis Research, (1997) Vol. 87, No. 1, pp. 123-129.
ISSN: 0049-3848.
AB Intramural thrombosis is a consistent finding in the arteries of patients who die following coronary angioplasty. This thrombosis is thought to have a role in restenosis, which is a common complication of coronary angioplasty. It has been hypothesised that antithrombotics such as **hirudin** or tissue -type plasminogen activator (tPA), may be therapeutically useful following angioplasty. This report describes the bioavailability of both agents following subcutaneous (sc) injection in cholesterol-fed rabbits. Intravenously delivered tPA has a **half-life** of 3-5 minutes. The **half-life** of intravenously administered **hirudin** is less than one hour in many species. In order to prolong the duration of action recombinant **hirudin** was conjugated to polyethylene glycol (**PEG**). Polyethylene glycol conjugated recombinant **hirudin** (**PEG** -rH) (0.7mg/kg) antigen and activity were measurable after just 1 hr, reaching a maximum (663 and 884 ng/ml respectively) at 12 hours. Significant levels were present in rabbit plasma 24 hours after injection. Subcutaneously delivered recombinant (r-tPA) (1mg/kg) was present in significant amounts 1hr after injection, reaching a maximum (92 IU/ml) at 2 hours. Levels of tPA at 9 hours were approximately 80x normal circulating levels. High and constant levels of functional activity of both **PEG**-rH and r-tPA in rabbit plasma are achieved by subcutaneous delivery.

L7 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PY 1993
AU Zawilska, K. (1); Zozulinska, M.; Turowiecka, Z.; Blahut, M.; Drobnik, L.; Vinazzer, H.
TI The effect of a long-acting recombinant **hirudin** (**PEG-hirudin**) on experimental disseminated intravascular coagulation (DIC) in rabbits.
SO Thrombosis Research, (1993) Vol. 69, No. 3, pp. 315-320.
ISSN: 0049-3848.
AB Reproducible disseminated intravascular coagulation in rabbits was provoked by two intravenous injections 24 hours apart of endotoxin from Salmonella enteritidis. There were mild symptoms of DIC before the second injection which considerably increased thereafter. In detail there was a sharp drop of the platelet count and a considerable diminution of Antithrombin III, of Protein C, Plasminogen and Antiplasmin as well as an appearance of fibrin monomer complexes and an increase of the aPTT. When **PEG-hirudin** in a single dose of 1 mg/kg BW was given simultaneously with the second injection of endotoxin the following

alterations were observed: The drop of the platelet count and of the activities of Antithrombin III, Protein C, Plasminogen and Antiplasmin was significantly less pronounced. The fibrin monomer complexes were lower and the aPTT was less prolonged. The thrombin time, however, as a sign of a direct action of **hirudin** on thrombin was considerably more prolonged than in the controls. The combined effect of these alterations strongly points in the direction of a favourable influence of **PEG -hirudin** on the course of DIC. It is of special interest that 6 h after the intravenous injection of **PEG-hirudin** its full effect on the thrombin time was still detectable. This is apparently due to a longer **half-life** in circulation of **PEG-hirudin** than of natural **hirudin**.

L7 ANSWER 9 OF 23 MEDLINE
PY 2001
AU Moser M; Ruef J; Peter K; Kohler B; Gulba D C; Paterna N; Nordt T; Kubler W; Bode C
TI Ecarin Clotting Time but not aPTT Correlates with **PEG-Hirudin** Plasma Activity.
SO JOURNAL OF THROMBOSIS AND THROMBOLYSIS, (2001 Oct) 12 (2) 165-9. Journal code: 9502018. ISSN: 0929-5305.
AB Background: Novel antithrombotic agents such as **hirudin** have shown promise in the therapy of acute coronary syndromes. **PEG-hirudin** (polyethyleneglycol conjugated **hirudin**) has been developed to provide a longer plasma **half-life** and more stable antithrombotic plasma levels. Privious trials indicated a narrow therapeutic window for **hirudin** and a number of aPTT (activated partial thromboplastin time)-monitored trials investigating **hirudin** in acute coronary syndromes had to be stopped because of intracranial bleeding complications.Objectives: The present study evaluates the ecarin clotting time (ECT), a parameter based on the conversion of prothrombin by the snake venom enzyme ecarin, for the monitoring of **PEG-hirudin** therapy.Methods: Plasma from either healthy volunteers (n=20) or from patients (n=10) suffering from unstable angina pectoris (UAP) was spiked with increasing **PEG-hirudin** concentrations. In a prospective randomized clinical trial patients with UAP were treated with intravenous **PEG-hirudin** or heparin over 72 hours. Patients were randomized to the following treatment groups: (1) heparin control group, n=15; (2) **PEG-hirudin** low dose (0.1[emsp4]mg/kg bolus, 0.01[emsp4]mg/kg/h infusion), n=19; (3) intermediate dose (0.15[emsp4]mg/kg and 0.015[emsp4]mg/kg/h), n=17; 4) high-dose (0.2[emsp4]mg/kg and 0.02[emsp4]mg/kg/h), n=16. Spiked plasma samples and plasma from UAP patients treated with i.v. **PEG-hirudin** were analyzed for aPTT, ECT, and **PEG-hirudin** levels.Results: A linear correlation up to the highest therapeutic concentrations could be observed between **PEG-hirudin** plasma concentrations and the ECT. This was true for both plasma samples spiked with **PEG-hirudin** in vitro as well as for samples taken from patients treated with i.v. **PEG-hirudin** (correlation coefficient 0.9, respect.) In contrast the aPTT did not show a reliable linear correlation to **PEG-hirudin** concentrations.Conclusion: Monitoring of **PEG-hirudin** therapy by ECT may help to avoid inadequate anticoagulation or overdosing. Thus, the safety and efficacy profile of **PEG-hirudin** therapy is likely to be enhanced by ECT monitoring.

L7 ANSWER 10 OF 23 MEDLINE
PY 2001
AU Avgerinos G C; Turner B G; Gorelick K J; Papendieck A; Weydemann U; Gellissen G

09921880

TI Production and clinical development of a Hansenula polymorpha-derived PEGylated **hirudin**.
SO SEMINARS IN THROMBOSIS AND HEMOSTASIS, (2001 Aug) 27 (4) 357-72. Ref: 44
Journal code: 0431155. ISSN: 0094-6176.
AB This article describes the expression of the **hirudin** gene heterologously in the methylotrophic yeast Hansenula polymorpha, the establishment of an industrial-scale production process and the subsequent clinical development of polyethylene glycol (**PEG**)-**hirudin**. PEGylation increases the molecular weight of **hirudin**, thereby reducing its kidney filtration rate and immunogenicity and increasing its **half-life** in the circulation.

L7 ANSWER 11 OF 23 MEDLINE
PY 2001
AU Kamler M; Chatterjee T; Stemberger A; Gebhard M M; Hagl S; Jakob H
TI **Hirudin** protects from leukocyte/endothelial cell interaction induced by **extracorporeal** circulation.
SO THORACIC AND CARDIOVASCULAR SURGEON, (2001 Jun) 49 (3) 157-61.
Journal code: 7903387. ISSN: 0171-6425.
AB BACKGROUND: The clinical complications of **Extracorporeal** Circulation (ECC) have been linked to disturbances in the microcirculation. In order to prevent these deleterious effects, a biodegradeable agent to coat the **extracorporeal** circuit was tested. METHODS: Intravital fluorescence microscopy was used on the hamster skinfold chamber model in permanently instrumented, awake animals. ECC was introduced via a micro-roller-pump and a silicon tube shunted between the carotid artery and the jugular vein. The ECC-tube system was coated with **PEG-Hirudin**-Iloprost, two additional groups received either Iloprost i.v. (0.8 mg/kg/h) or **Hirudin** i.v. (1 mg/kg b.w.). RESULTS: ECC for 20 minutes resulted in an increase in rolling and adherent leukocytes in postcapillary venules (Roller 9 to 36 [%]; Sticker 24 to 330 [n/mm2]). Use of the coated tube system reduced L/E cell interaction (Roller 9 to 24* [%], Sticker 28 to 194* [n/mm2]; *$p<0.05$), whereas **Hirudin** i.v. nearly abolished it. CONCLUSIONS: The protective effects of the coating and of **Hirudin** i.v are probably a result of an attenuated activation of the coagulation-fibrinolytic system.

L7 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 2001
2002
IN Scherhag, Rudi; Bacher, Peter; Parow, Christopher; Esslinger, Hans-Ulrich; Abel, Florian
TI Anticoagulants in the **extracorporeal** treatment of blood
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
AB The present invention relates to the use of anticoagulant agents, and in particular of **PEG-hirudin**, for treating individuals with **extracorporeal** circulation for prophylaxis of vascular complications after the **extracorporeal** circulation. It is thus possible in particular to treat individuals with chronic **renal** insufficiency requiring regular **hemodialysis** and moreover prevent vascular complications which conventionally result in a high morbidity and mortality rate for **dialysis** patients treated longer-term. Thus, 20 male and female patients between 18 and 75 yr who must regularly undergo **hemodialysis** were selected. After an initial treatment with heparin, each patient was given an i.v. injection, immediately before the first **dialysis** during **PEG-hirudin** treatment, of a dose of 0.08 mg/kg of **PEG-hirudin** with a specific antithrombin activity of 13,354 ATU/mg of

protein/kg of body wt. This was followed by **hemodialysis** with an av. duration of 4 h. The residual **PEG-hirudin** concns. initially increased and allowed the dose to be reduced from the initial 0.08 to 0.03-0.05 mg/kg of body wt. This dosage was suitable for obtaining blood levels of **PEG-hirudin** in the range 500-1000 ng/mL of whole blood on completion of each **dialysis** with 3 **hemodialysis** a week.

L7 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 2001
AU Kamler, M.; Chatterjee, T.; Trojansky, M.; Stemberger, A.; Gebhard, M. M.; Hagl, S.; Jakob, H.
TI Reduction of Leukocyte/Endothelial cell interaction induced by **Extracorporeal** Circulation with the use of a coated tube system
SO Materialwissenschaft und Werkstofftechnik (2001), 32(2), 154-159
CODEN: MATWER; ISSN: 0933-5137
AB The clin. complications of **Extracorporeal** Circulation (ECC) have been linked to disturbances in the microcirculation. In previous expts. we found in vivo an increased Leukocyte/Endothelial (L/E) cell interaction following ECC. As a therapeutic approach to prevent these deleterious effects a new agent, incorporating **Hirudin** and Prostacyclin, to coat the tubing system was used. Intravital fluorescence microscopy was used on the dorsal skin-fold chamber prepn. in syrian golden hamsters. ECC was introduced via a micro-roller pump (1 mL/min) and a 60 cm silicon tube (1 mm inner diam.) shunted between the carotid artery and the jugular vein. Expts. were performed in chronically instrumented, awake animals (age: 10-14 wk, wt.: 65-75 g). Control tubes were uncoated, for the expt. a **PEG-Hirudin**-Iloprost coating was used. Isovolemic ECC for 20 min resulted in an increase in rolling (BL: 9% .+-. 2; after 4 h: 36%* .+-. 5; mean .+-. SD, *p < 0.05) and adherent leukocytes (BL: 24.+-.26; after 4 h: 260* .+-. 51; mean .+-. SD; p < 0.05) in postcapillary venules. The use of the coated tube system resulted in a less pronounced induction of leukocyte/endothelial cell interaction. Microhemodynamic parameters and functional capillary d. were not significantly affected. Arterial blood pressure and heart rate were stable. L/E interaction in the microcirculation has been established as an indicator of the systemic activation induced by blood contact to synthetic surfaces during ECC. Coating the **extracorporeal** circuit reduced the increase in L/E interaction probably as a result of an attenuated activation of the coagulation-fibrinolytic system including a reduced platelet activation.

L7 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 2000
2000
2001
2002
IN Nowak, Gotz; Bucha, Elke
TI Use of extended-molecular weight **hirudin** as anticoagulant during artificial kidney therapy
SO Ger. Offen., 6 pp.
CODEN: GWXXBX
AB Extended-mol.-wt. **hirudins** are disclosed for the prepn. of non-autoimmune disease-inducing, non-autoantibody-crossreacting anticoagulants for artificial kidney therapy. In particular, no type II thrombocytopenia is caused, and no crossreactivity with antibodies against platelet factor 4-heparin-complex is seen. The extended-mol.-wt. **hirudins** of the invention include e.g. **hirudin** conjugated with polyethylene glycol.

L7 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2002 ACS

09921880

PY 1999
AU Chatterjee, T.; Kamler, M.; Jakob, H.; Stemberger, A.; Gebhard, M. M.; Hagl, S.
TI Effects of **extracorporeal** circulation on the microcirculation in vivo. Influence of the contact activation
SO Laboratoriumsmedizin (1999), 23(6), 368
CODEN: LABOD3; ISSN: 0342-3026
AB The protective effects of **PEG-hirudin**-Iloprost tube coating from **extracorporeal** microcirculation induced contact activation of leukocytes were studied. The model of hamster back chamber was proved to be suitable for the visualization and quantification of **extracorporeal** microcirculation induced disturbances as well as for the examn. of the therapeutical effects of potential intervention strategies.

L7 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 1998
2000
1998
1998
2000
2001
2002
IN Bucha, Elke; Nowak, Goetz
TI PMMA membranes with polyethylene glycol-bound physiologically active substances
SO Ger. Offen., 10 pp.
CODEN: GWXXBX
AB A PMMA membrane or copolymer membrane with **PEG**-bound physiol. active substances is used as a functional antidote (e.g., contg. antibodies, enzymes, anticoagulants, tumor markers) in **extracorporeal** therapeutic systems, e.g., blood **dialysis** systems. The **PEG**-bound active substance binds to the membrane. In examples, **hirudin** anticoagulants, **hirudin** monoclonal antibodies, monoclonal antibodies to tumor necrosis factors, and urease were bound to **PEG** and utilized in PMMA capillary **dialysis** systems for blood treatment.

L7 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 1997
AU Fenton, Brian; Lauziere, Kevin; Welch, Jeffrey; Crowley, Richard; Licari, Peter; Ruebsamen, Klaus; Turner, Brian
TI Manufacturing, characterization, and pharmacokinetics of a monodisperse **PEG-Hirudin**
SO Polymer Preprints (American Chemical Society, Division of Polymer Chemistry) (1997), 38(1), 570-571
CODEN: ACPPAY; ISSN: 0032-3934
AB A monodisperse, fully active **PEG-hirudin** with prolonged circulatory **half-life** in rabbits was obtained by coupling PEG5000 to a recombinant **hirudin** contg. two lysine residues per mol. This product is presently being developed clin. in humans for a no. of indications.

L7 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 1997
AU Fenton, Brian; Lauziere, Kevin; Welch, Jeffrey; Crowley, Richard; Licari, Peter; Ruebsamen, Klaus; Turner, Brian
TI Manufacturing, characterization, and pharmacokinetics of a monodisperse **PEG-hirudin**.
SO Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), POLY-186 Publisher: American Chemical Society, Washington, D. C.

CODEN: 64AOAA

AB The 65 amino acid polypeptide **hirudin** is a potent thrombin inhibitor, but its relatively short circulatory **half-life** limits its usefulness in certain clin. indications. Coupling of **PEG** to native **hirudin** is one approach to increasing **half-life**, but the result is a polydisperse population of mols., some of which are biol. inactive or have excessively long **half-lives**. We instead elected to manuf. a well-defined, monodisperse **PEG-hirudin** for clin. development. Our approach was to couple PEG5000 to a recombinant **hirudin** contg. fewer lysine residues than native **hirudin** to minimize heterogeneity, then purifying the clin. useful form of **PEG-hirudin**. Recombinant **hirudin** was secreted from cultures of Hansenula polymorpha and purified to homogeneity. Following coupling with activated **PEG**, the desired form of **PEG-hirudin** was purified using anion exchange and hydrophobic interaction chromatog. The result is a fully active, monodisperse product contg. two moles of **PEG** per mol of **hirudin**. We will present an overview of the manufg. process, physicochem. characterization results, and in vivo data comparing the pharmacokinetics of **hirudin** and **PEG-hirudin**.

L7 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2002 ACS
PY 1993
2002
1993
1995
1994
1993
2002
1994
IN Bischoff, Rainer
TI Polyethyleneglycol peptide conjugates, method of preparation, and use in pharmaceuticals
SO Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
AB A method for prepg. a peptide-**PEG** conjugate, esp. a **PEG-hirudin** conjugate, comprises activation of **PEG** with carbonyldiimidazole, N-hydroxysuccinimide, or 2,3,5-trichloroformate in an anhyd. solvent; collection of the activated **PEG** by pptn. with a hydrophobic org. solvent; and reaction of the peptide with the activated **PEG**. The method is simple, rapid, and applicable to industrial prepns. Thus, recombinant [Lys-47]**hirudin** was reacted with carbonyldiimidazole-activated **PEG** to prep. a **hirudin-PEG** conjugate. The activated **PEG** was prepd. from **PEG**-50,000 in dioxane, and was pptd. with Et ether. The yield of **hirudin-PEG** conjugate was 63-88%. The Ki for thrombin was unaltered by this modification, but the serum **half-life** was significantly increased.

L7 ANSWER 20 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
PY 2001
AU Avgerinos G.C.; Turner B.G.; Gorelick K.J.; Papendieck A.; Weydemann U.; Gellissen G.
TI Production and clinical development of a Hansenula polymorpha-derived PEGylated **hirudin**.
SO Seminars in Thrombosis and Hemostasis, (2001) 27/4 (357-371).
Refs: 44
ISSN: 0094-6176 CODEN: STHMBV
AB This article describes the expression of the **hirudin** gene heterologously in the methylotrophic yeast Hansenula polymorpha, the

establishment of an industrial-scale production process and the subsequent clinical development of polyethylene glycol (**PEG**)-**hirudin**. PEGylation increases the molecular weight of **hirudin**, thereby reducing its kidney filtration rate and immunogenicity and increasing its half-life in the circulation.

L7 ANSWER 21 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
PY 2000
AU Mustafa M.Ua.; Kadr H.; Kemp M.; Hooper J.; Shaw S.; Stephens J.D.
TI **PEG-hirudin** compared with unfractionated heparin reduces the burden of silent ischaemia in unstable angina and non-Q-wave MI.
SO British Journal of Cardiology, (2000) 7/12 (771+774-775+777).
Refs: 29
ISSN: 0969-6113 CODEN: BJCAEM

L7 ANSWER 22 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
PY 2000
AU Friederich P.W.; Keller T.T.; Biemond B.J.; Peters R.J.G.; Hornberger W.; Buller H.R.; Levi M.
TI Successful attenuation of venous thrombus growth in rabbits after the administration of a novel oral thrombin inhibitor.
SO Thrombosis and Haemostasis, (2000) 84/5 (858-864).
Refs: 46
ISSN: 0340-6245 CODEN: THHADQ
AB Current antithrombotic compounds have several limitations in clinical practice. The present study was designed to investigate a novel orally available direct thrombin inhibitor, BSF 208791. Intravenous administration of BSF 208791 showed superior antithrombotic properties as compared with Polyethylenglycol-**Hirudin** (**PEG-Hirudin**) and low molecular weight heparin (LMWH) in a model of venous thrombosis in rabbits. The thrombus growth was 22%, 30%, 37% and 50% after BSF 208791, **PEG-Hirudin**, LMWH, and saline administration, respectively. Moreover, bleeding time was less affected after administration of BSF 208791 as compared with **PEG-Hirudin**. The oral administration of BSF 208791 resulted in adequate bioavailability and significantly reduced venous thrombus growth to 36% as compared with 60% in the saline treated rabbits. The antithrombotic effect of BSF 208791 appears to be superior to **PEG-Hirudin** and LMWH without affecting the bleeding time. BSF 208791 is an orally available agent that might be a promising candidate for future antithrombotic therapy.

L7 ANSWER 23 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
PY 1997
AU Stein G (Reprint); Bucha E; Poschel K; Jansa U; Schindler S; Esslinger H U; Nowak G
TI Pharmacokinetics of **PEG-hirudin** in patients with chronic **renal** failure.
SO JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (SEP 1997) Vol. 8, Supp. [S], pp. A0368-A0368.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 1046-6673.

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---Logging off of STN---

09921880

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	61.34	63.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.96	-4.96

STN INTERNATIONAL LOGOFF AT 14:36:04 ON 16 AUG 2002

	S arch T rms	Total
1	CIRCULATION	226945
2	CIRCULATIONS	2187
3	EXTRACORPOREAL	7936
4	HIRUDIN	1913
5	HIRUDINS	103
6	PROPHYLACTIC	25733
7	PROPHYLACTICS	776
8	TREATMENT	1309073
9	TREATMENTS	125843
10	(L34 AND HIRUDIN)	3

	Search Terms	Total
1	ANTICOAGULANT	11119
2	ANTICOAGULANTS	4857
3	APTT	1123
4	APTTS	31
5	CIRCULATION	226945
6	CIRCULATIONS	2187
7	EXTRACORPOREAL	7936
8	HEPARAN	1675
9	HEPARANS	11
10	HIRUDIN	1913
11	HIRUDINS	103
12	PROPHYLACTIC	25733
13	PROPHYLACTICS	776
14	(L58 AND APTT)	7

	S arch Terms	Total
1	ANTICOAGULANT	11119
2	ANTICOAGULANTS	4857
3	HIRUDIN	1913
4	HIRUDINS	103
5	PEG	52103
6	PEGS	22647
7	(L88 AND ANTICOAGULANT)	12

	Search Terms	Total
1	ADMINISTER	45329
2	ADMINISTERED	165753
3	ADMINISTEREDS	1
4	ADMINISTERING	118152
5	ADMINISTERINGS	5
6	ADMINISTERS	2769
7	ANTICOAGULANT	11119
8	ANTICOAGULANTS	4857
9	CHRONIC	56174
10	CHRONICS	3
11	DOSAGE	147655
12	DOSAGES	49730
13	DOSE	199335
14	DOSES	98405
15	HEMODIALYSI	6
16	HEMODIALYSIS	4371
17	HEPARAN	1675
18	HEPARANS	11
19	HIRUDIN	1913
20	HIRUDINS	103
21	RENAL	29079
22	RENALS	67
23	(((HEMODIALYSIS AND (HEPARAN OR HIRUDIN) AND ANTICOAGULANT) AND (RENAL NEAR CHRONIC)) AND (ADMINISTER OR ADMINISTERING OR DOSAGE OR ADMINISTERED OR DOSE))	23